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ATTY. DOCKET NO.: 10503/P61750US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

WENDEL et al.

Group Art Unit: 1641

Serial No.: 08/996,768

Examiner: J. HINES

Filed: December 23, 1997

For: TEST PROCEDURE WITH BIOLOGICAL SYSTEM

RESPONSE

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants submit the instant Response to the Office action mailed January 4, 2000.

Claims 19-25 and 27-29 are presented for consideration.

Applicants wish to thank the Examiner for the careful consideration rendered in reviewing the file pursuant to Applicant's request to withdraw the Final action.

In accordance with the instant Office action, claims 19-29 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Reconsideration is respectfully requested.

According to this statement of rejection, claims 19-29 are indefinite because the claims do not include "a correlation step that relates the immunofunctional, toxic and/or modulatory reaction to the exposure to test materials." With all due respect,

Applicants submit that claims 19-29 are complete and they satisfy the standards of 35 USC 112, second paragraph.

The preamble of claim 19 recites that the claimed method is for "determining the reaction of blood to test materials and objects for human applications." The final step of the claimed method recites "detecting and/or measuring the immunalfunctional, toxic, and/or modulatory reaction of the sample of whole blood to said material or object biological, physical, chemical, and/or physicochemical methods."

Accordingly, the last step of claim 19 is fully commensurate with the preamble of the claim, in that the preamble recites a *method for determining the reaction of blood to test materials and objects*, and the last step of the claim recites *detecting and/or measuring the ... reaction of the sample of whole blood to said material or object*. Put simply, the claim preamble requires no more than determining the reaction, and the final step of the claim does just that.

Claims were rejected under 35 USC 103 based on the combined teachings of Wendel and Boyse. Claims were further, rejected under 35 USC 103 based on the combined teachings of Wendel, Boyse, and Dinarello. Reconsideration of the aforesaid rejections under §103 is respectfully requested.

The Wendel process is an analytical procedure to test substances for pyrogenicity. As an example, any pharmaceutical charge has to be tested for pyrogenicity before marketing according to EU laws. The "rabbit" test and the limulus test are unsatisfying because inherently unspecific, incomplete and time consuming. The Wendel/Hartung test procedure is fast, is highly specific to humans and is covering gram negative and gram positive based pyrogens by using whole (human) blood and measuring endogenous pyrogen blood response. The test is besides being specific highly sensitive because it is performed in presence of any and all blood compounds, possibly influenced by pyrogens. Wendel/Hartung mention only fresh whole blood or preparations containing fresh whole blood (see example). In spite of all advantages of the procedure problems may arise from the necessity of fresh blood, described in details in the present specification (e.g. danger of using blood of an unsuitable donor under "emergency" conditions, problems with the comparability of a test with earlier tests and so on).

The instant, claims directed to an analytical method for testing materials and objects for human applications, readily distinguish the cited prior art by two main features:

- the sample of whole blood is a sample of thawed, cryopreserved whole blood (including whole blood preparations containing f. i. anticoagulants, solvents or cryopreservatives)

- the sample of thawed cryopreserved whole blood is a unit of a large number of identical cryopreserved units of one lot of whole blood (including whole blood preparations of one lot of whole blood).

Applicants respectfully submit that combining this subject matter as in the instant claims is neither taught nor suggested by the cited references, taken alone of in combination.

Boyse et al. US '681, and the almost identical Boyse et al US '553, are directed to stem and progenitor cells of neonatal or fetal blood that are cryopreserved and the therapeutic use of such stem and progenitor cells upon thawing (Boyse, '681, Abstract; col. 8, lines 23-26; col. 10, lines 8-11; Boyse '553, col.8, lines 43-46; col. 10, lines 28-31). Adult blood contains very few of such cells ('681, col. 3, lines 42-44; '553, col. 3, lines 47-49): neonatal or fetal cells provide distinct advantages over adult peripheral blood ('681, col 11, lines 11-14, 27, 28; '553, col. 11, lines 32, 33,

47, 48). Sources for Boyse's stem and progenitor cells are neonatal or fetal blood ('681, col. 12, lines 41, 42; '553, col. 12, lines 60, 61) and the cells are separated from or enriched in such blood ('681, col. 12, line 38; col 22, line 23; '553, col. 12, line 57, col 22, line 53). Freezing of cells is said to be ordinarily destructive ('681, col. 22, line 26; '553, col. 22, line 56). Use of cryoprotective agents, control of freezing rate and storage at low temperatures is recommended ('681, col. 22, lines 35-38; '553, col 22, lines 65-68). Cryopreservation of stem and progenitor cells from cord blood results, after thawing, to cell losses up to 86.5% ('681 and '553, Table V. CB 17) and an average survival of cells of 36.1% (Table V).

According to the statement of rejection Boyse's thawed cryopreserved neonatal or fetal blood cells can be used for autologous reconstitution. The rejection maintains that cryoprotective agents and optimal cooling rates can protect cells against injury. Whole neonatal blood cryopreserved and thawed, can be used for therapy, according to the rejection. Applicants respectfully submit that the rejection misses important facts.

Both Boyse patents deal with thawed and cryopreserved neonatal or fetal stem and progenitor cells including whole blood containing such cells; they mention exclusively the *therapeutic* use of such products ('681), Abstract; col. 8, lines 23-37; col. 10, lines 8-11; col 26, line 35 - col. 33, line 34; '551, Abstract; col. 8, lines 43-

57; col. 10, lines 28-31; col 26, line 65 - col. 33 line 58). The rejection's repeated "can" be used is, with all due respect, misleading. Neither Boyse patent gives the slightest hint for any use other than therapy.

The survival rate of Boyse's cells after cryopreservation and thawing would be as little as about 15-35% and never beyond 67% (Table V).

Both Boyse patents are trying to isolate human neonatal or fetal stem or progenitor cells from blood and to cryopreserve the cells, even for years, for later therapeutic uses ('681, col. 30, lines 32-36; col. 31, lines 11-16; '553, col. 31, lines 27-31; col. 32, lines 6-11). Both Boyse patents are using neonatal or fetal whole blood like a "carrier" for their stem cells, disregarding and without taking care or making use of all the other, major constituents of whole blood, irrespective of whether plasma or monocytes are present or not. For the purpose of Boyse et al., the only fact that matters is to cryopreserved stem or progenitor cells in more or less concentrated form and after thawing to infuse it for therapy. This is what Boyse teaches for a person skilled in the art.

Dinarello deals with an analytic process, a pyrogen test. To perform this test he is incubating the substance for at least 46 hours with a cell mixture of lymphocytes and monocytes, at a cell ratio of at least 2:1, with the specified minimum of monocytes and no more than 10% granulocytes and with the defined cell contact ratio

(col. 3, lines 10-20). The cells to be used have to be isolated from blood in a more or less cumbersome way (col. 4, line 42 - col. 5, line 32; col. 13, lines 22-67). Care has to be taken that the cells are free of extraneous material from the original blood sample (col. 5, lines 26-34), only small amounts of additional types of cells being permissible. Cell mixtures with a ratio of less than 2:1 are discarded (col. 5, lines 58-60). (Whole blood contains large amounts of non-cellular matter, a lymphocytes to monocytes ratio of 5:1 and about 60% granulocytes). Dinarello is teaching away from whole blood, certainly not using or recommending to use whole blood, let alone using thawed cryopreserved whole blood.

Wendel and Dinarello are dealing with an analytical process. Boyse '681 as well as Boyse '553 are dealing with a therapeutical method. Wendel and Dinarello are testing substances and materials for pyrogenicity. Both Boyse patents are using neonatal or fetal separated or enriched stem or progenitor cells as a pharmaceutical for therapeutic use. No person skilled in the art concerned with the improvement of an analytical process would direct his attention to a therapeutical treatment where neonatal or fetal stem or progenitor cells are applied, cryopreserved, and thawed in order to make a pharmaceutical.

Wendel uses in his analytical process whole blood, which gives access to highly specific and fully reliable data. Dinarello is not even using whole blood, but goes the

troublesome circuitous route of isolating two components and making, thereby, room for possible errors. Both Boyse patents are exclusively interested in and use neonatal or fetal stem or progenitor cells – which can also be separated, enriched, or gene-modified – from neonatal or fetal blood and in cryopreserved form, to keep this cells viable for a long time.

Thus, cryopreserved stem cell compositions could be prepared at birth and given to the same person as an adult as a pharmaceutical. Also, cell compositions could be prepared while the person is still healthy; and, should the person later develop cancer, his own cells are administered to him, therapeutically, after cytostatic chemotherapy (Boyse '681: col. 29, lines 62-69: col. 30, lines 32-36; col. 31, lines 11-16; Boyse '553, col. 31, lines 27-31; col. 32, lines 6-11).

Both Boyse patents make use only of a small group of blood cells, disregarding – and even discarding – all other, i.e., the majority, of blood constituents. This, again, is leading away from the presently claimed invention. The instant claims require (are limited to) whole blood; unless whole blood is used, the required results would not be obtained.

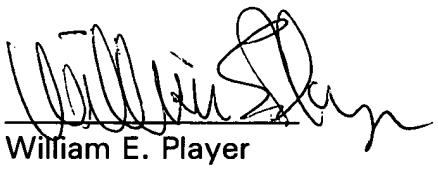
Furthermore, any person skilled in the art reading both Boyse patents would be urged to avoid cryopreservation, in view of the drastic changes and losses of blood cells reported by these patents. These negative effects, reported in Boyse Table V,

might be acceptable for the (purposes of) Boyse cells; but, such effects are a strong warning when use has to be made of all components of the whole blood. With all due respect, the statement of rejection is clearly wrong in saying "frozen blood is protected against cellular injury"; both Boyse patents teach the opposite.

Finally, the instant claims are not only directed to the specified analytical method wherein thawed cryopreserved whole blood is used. None of the references cited teach or suggest the second, important aspect of the presently claimed analytical process: The cryopreserved whole blood is a unit of a large number of identical cryopreserved units of one lot of whole blood.

Favorable action is requested.

Respectfully submitted,
JACOBSON, PRICE, HOLMAN & STERN, PLLC



William E. Player
Registration No. 31,409

400 Seventh Street, N.W.
Washington, D.C. 20004
Telephone: (202) 638-6666
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